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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/556,901	02/02/2006	Mark Ashton	BJS-620-401	1869

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EXAMINER	
CHANDRAKUMAR, NIZAL S	
ART UNIT	PAPER NUMBER
1625	

MAIL DATE	DELIVERY MODE
04/09/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/556,901	ASHTON ET AL.	
	Examiner	Art Unit	
	NIZAL S. CHANDRAKUMAR	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-9,11,12,31,34,37-39,44-48 and 51-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 6-9, 11-12, 31, 34, 37-39, 44-48, 51-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicants Response filed 02/23/2009 response was in response to restriction requirement 01/22/2009 which was filed subsequent to discussion with B.J.Sadoff, attorney for the applicants. In the discussion, as noted at the out set of the papers filed 01/22/2009, the Examiner agreed for the new restriction requirement because of the typographical error in the requirement filed 11/19/2008.

Applicant's election with traverse of Group I in the reply filed on 02/23/2009 is acknowledged. The traversal is on the ground(s) that the requirement is improper and inappropriate at the present time (after having previously presented office actions on the merits).

This is found persuasive and the requirement is withdrawn.

Pending claims:

Claims 31, 34, 37-39, 44-48, 51-54 are drawn to compounds of the given formulae.

Claims 1-4, 6-9, 11-12, drawn to methods of treating condition which can be alleviated by the inhibition of glyoxalase I, using compounds of the given formulae.

This present office action pertains to Examination on merits of all pending claims 1-4, 6-9, 11-12, 31, 34, 37-39, 44-48, 51-54. Since the previously presented restrictions are withdrawn, this office action is also responsive to

applicants remarks filed 10/01/2008 in response to the previously presented office action on merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Previously presented rejection pertaining to 'solvates' and C5-6 arylene is withdrawn in view of applicant's remarks.

Claims 34 and 51 and dependent claims 31, 37-39, 44-48, 52-54 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 34 and 51 are drawn to C7 aryl group. The scope of this monovalent substituent is unclear. For instance, one skilled in the art would recognize a C7 aromatic with 7 ring atoms (see below) as a tropylium ion. If such a moiety is a substituent in a compound, the compound would require a counter ion, in this case a negative ion. This is not pictured in the given formulae. Applicant's definition of C5-7 aryl is given below:

> [0108] C_{5-7} aryl: The term "C_{5-7} aryl" as used herein, pertains to a monovalent moiety obtained by removing a hydrogen atom from an aromatic ring atom of an aromatic compound, which moiety has from 5 to 7 ring atoms (unless otherwise specified).
>
> [0109] In this context, the prefixes (e.g. C_{5-7}, C_{5-6} etc.) denote the number of ring atoms, or range of number of ring atoms, whether carbon atoms or heteroatoms. For example, the term "C_{5-6}aryl" as used herein, pertains to an aryl group having 5 or 6 ring atoms. Examples of groups of aryl groups include C_{5-7} aryl, C_{5-6} aryl, C_5 aryl and C_6aryl.

Claim 51 and the dependent claims are rejected because the formula II pictures I next to the chemical formula. The significance of this limitation I is unclear.

Claim 51 and the dependent claims are also rejected because the variable R6 is undefined and as such the scope of these claims is unclear.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Previously presented rejection of claims 31, 34, 37-39, 44-48 under 35 U.S.C. 112, first paragraph, as being enabling for making two compounds (two carboxylic acids, and two alleged prodrug esters of the corresponding acids) of the given formulae, does not reasonably provide adequate enablement for making representative members of the wide variety of structural possibilities

encompassed by the given formulae is maintained. Applicant's arguments were fully considered. (This office action, for reasons mentioned under section Election Restriction, would respond to applicant's arguments as well as provide additional reasons for rejection). Chemistry direction relevant to the instantly claimed compounds is shown in the form of Scehme-3, Scheme-5 (page 40 and 42 of the specification) and in discussions pertaining to these schemes. As discussed below, the guidance derivable from this scheme is limited to making a narrowly definable member of an overabundance of possibilities encompassed by the formulae. The formulae are also drawn to unknown solvates of the compounds of the formulae as well as substituents such as C7 aryl (see rejections under 112-2). The specification refers extensively to Text Book teachings in lieu of enabling direction, guidance and working example.

Claims 1-4, 6-9, 11-12 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the above mentioned two closely related compounds, does not reasonably provide enablement for the wide varieties of structural templates encompassed by the formulae. It is respectfully submitted that the very limited data provided in Tables 2 and 3 (page 56 and page 57) are inconsistent at best. One skilled in the art would find the data not representative of and not predictive (see reference cited below) of the plethora of possibilities encompassed by the formulae. As such, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The determination that "undue experimentation" would have been

needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the relevant factual considerations.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). 1) The breadth of the claims, 2) The nature of the invention, 3) The state of the prior art, 4) The level of one of ordinary skill, 5) The level of predictability in the art, 6) The amount of direction provided by the inventor, 7) The existence of working examples, 8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

All of the factors have been considered with regard to the claims, with the most relevant factors discussed below in the context of applicants Remarks filed 10/01/2008. Applicants arguments can be summarized as follows: The Examiner's rejection is based on unsupported conclusions and that Examiner is not believed to have demonstrated that compounds within the scope of the claims can not be prepared with reasonable experimentation. The rejection on the basis that the biological activity of the compounds claimed can not, allegedly, be extrapolated based on the (structurally similar) examples in the application.

Applicant's specific arguments:

Preparation of the Claimed compounds (See applicants Remarks page 11, last paragraph):

1. Applicant states that Table 4 of the application provides evidence

that compounds having high structural similarity to the claimed compounds may be readily obtained from commercial sources.

2. Further, page 12, second paragraph, applicant states that the examples found on page 38 onwards, provide guidance as to the type of transformations that are possible and predictable on a core structure which is highly similar to the claimed compounds. Further, the chemistry for hydroxylamide formation at the benzylic position can be extended to the formation of other hydroxylamide forms, absent contrary evidence from the Examiner.

3. Text book (page 13, of the remarks) teachings provide guidance, such as protective group strategy, to one skilled in the art to make compounds of the formulae.

Response:

1. Table-4, pages 58-61: Of the 35 compounds presented in the Table-4 **none** correspond to the structural core of the instant claims. At the minimum, the obligatory presence of hydroxylamide function N(OH)C(=O) as a mandatory claim limitation distinguishes the compounds from the compounds of Table-4 because none of the compounds of the compounds of Table-4 has this crucial hydroxylamide functionality. As such Examiner respectfully submits that arguments based on the commercial availability of the compounds of Table-4 are not indicative of the accessibility of the compounds of the instant claims. Parenthetically, except for compound 3, none of the

compounds of Table-4 would even be classified under the same class and subclass of the US patent classification system.

2. Teachings on page 38 onwards: For reasons similar to the ones in the above paragraph, Examiner submits that the applicant's arguments are not persuasive. The Scheme-1 and Scheme-2 in the pages 38 and 39 are drawn to *unrelated* pyridine compounds with *unrelated* disposition of the functionalities, unrelated because of the *instant* claim limitation. The core structure of compounds of the instant claims differ markedly from the structures compounds for which guidance and direction are presented in pages 38 and 39. Likewise, Scheme-5 on page 42, has no relevance to enabling disclosure pertaining to instantly claimed compounds as this scheme-5 and accompanying discussions relate to R4 possibilities *unrelated* to the instant claim limitation.

Though Scheme-4, page 41 teaches preparation of compounds *unrelated* to the instant claims, the benzylic substitution taught in this scheme is of relevance to the instant claim limitation. Relating to this teaching in Scheme-4 is the chemistry taught in Scheme-3.

Scheme-3, present on page 49 is relevant to the instant claims and in combination with the teachings in Scheme-4, is enabling for making compounds in which L4 is C1-alkylene to the carbon of which is connected the nitrogen of the crucial hydroxylamide function. Despite the benzylic nature of the substitution, Examiner agrees with applicants arguments that the

transformation of a hydroxy group to the hydroxylamide function is predictable.

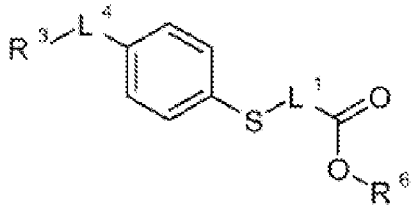
3. Text Book Teachings: Examiner agrees with the applicant that Text Books teach many chemical transformation as well as protective group strategies and organic synthesis depends on predictable transformations. Examiner agrees that such generalizations are consistent with the accomplishments in organic synthesis. But the instant rejection is in the context of 112-1 requirements, whether *undue* effort would be required to make the compounds of the instant claims. Further Text Books also teach the unpredictability in the art of organic chemistry. See for example, Dorwald F. A. Side Reactions in Organic Synthesis, 2005, Wiley: VCH, Weinheim pg. IX of Preface pg. 1-15.. Dorwald et al. states, "Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that

originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work……Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious) [preface]…….even structurally simple compounds often turn out not to be so easy to make as initially thought. [pg. 2]…….. As illustrated by the examples discussed below, a good retrosynthesis requires much synthetic experience, a broad knowledge of chemical reactivity, and the ability to rapidly recognize synthetically accessible substructures [pg. 3]…….. As will be shown throughout this book, the outcome of organic reactions is highly dependent on all structural features of a given starting material, and unexpected products may readily be formed. [8]……...Even the most experienced chemist will not be able to foresee all potential pitfalls of a synthesis, especially so if multifunctional, structurally complex intermediates must be prepared. The close proximity or conformational fixation of functional groups in a large molecule can alter their reactivity to such an extent that even simple chemical transformations can no longer be performed. Small structural variations of polyfunctional substrates might, therefore, bring about an unforeseeable change in reactivity [pg. 9]….."

Recast of previously presented rejection in view of the withdrawal of restriction/requirement.

The nature of the invention: This invention relates to compounds that by virtue of their ability to bind to the protein glyoxalase I, inhibit glyoxalase I and thereby provide for treatment to various conditions alleviated by the inhibition of glyoxalase I.

The breadth of the claims: The claims are drawn to compounds of the Formula I



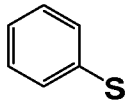
wherein L1 and L4 are

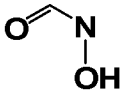
L^1 is optionally substituted [[C_{1-4} alkylene,]] C_{5-6} arylene, C_{1-4} alkylene-C_{5-6} arylene or $-L^5N(R^5)L^6-$, or C_{1-4} alkylene substituted by either C_{1-7} alkyl or C_{5-7} aryl, wherein L^5 and L^6 are independently selected from optionally substituted C_{1-4} alkylene and C_{5-6} arylene, and R^5 is H or C_{1-4} alkyl;

R^6 is selected from H or optionally substituted C_{1-7} alkyl, C_{5-6} aryl and C_{1-4} alkylene-C_{5-6} aryl;

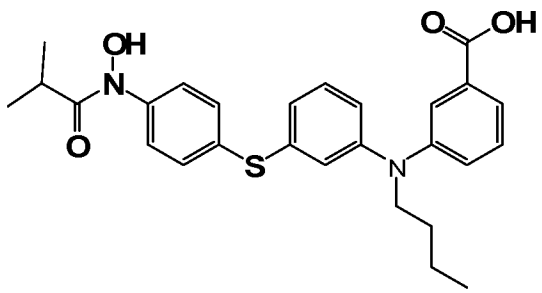
L^4 is independently selected from $-L^9YN(OH)C(=O)L^{10}-$ and $-L^9C(=O)N(OH)YL^{10}-$, wherein L^9 and L^{10} are independently selected from optionally substituted C_{1-4} alkylene, C_{5-6} arylene, C_{1-4} alkylene-C_{5-6} arylene and a single bond, wherein Y is NH or a single bond.

Thus the given formulae encompass compounds that can be assembled by the union of three structural elements:



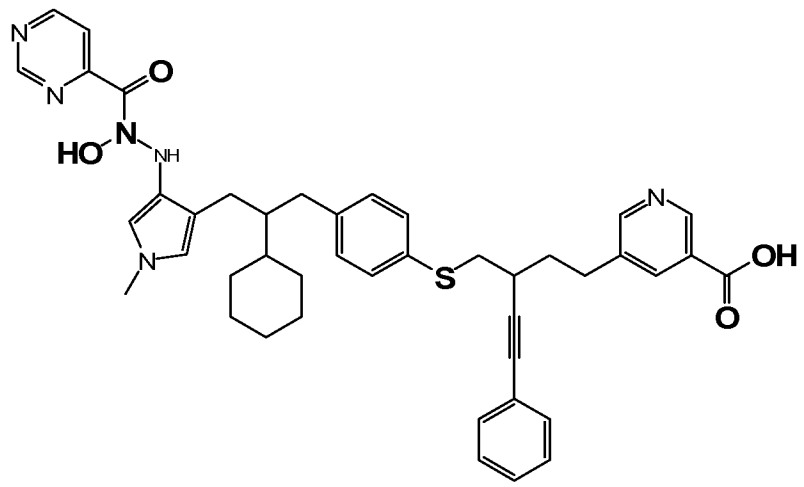


These units are connected by a wide variety of linkers (2-dimensional and 3-dimensional linkers, that by moieties that are flat (2-D) as in arylene or tetrahedral 3-D linkers as in alkylenes/cycloalkylenes) defined by L1 and L2 and flanked by a wide variety of end groups defined by R3 and R6, with substituents layered on top of substituents leading to infinite number of structural possibilities. One skilled in the art would anticipate that such a scope to encompass molecules that widely vary in the physical and chemical properties such as size (see below for examples of structural possibilities), molecular weight, logP, acidity and basicity. These properties that are known in the art to greatly influence the PK and PD parameters, cell permeability (particularly important in the intended use of the compounds see Thornalley reference cited below), not to mention the ability of the molecules to productively bind to glyoxalase I. In addition the claims are also drawn to undisclosed solvates and substituent such as C7 aryl, esters of various alcohols, rendering the scope of the claims large. Thus, for example the claimed formulae (also see paragraph 77-79 of published application for definitions optional substituents) include such widely different structures as,



C1

and



C2

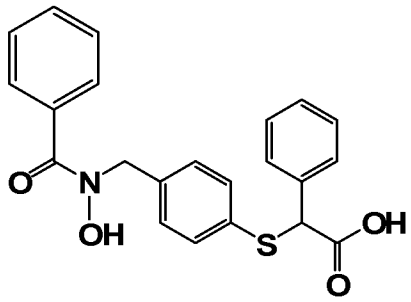
[The above description depicts what appears to be the minimum pharmacophoric groups (highlighted in bold) necessary for binding to glyoxalase I]

The level of skill in art and predictability in the art: Though organic synthesis relies on predictable chemical transformations, in spite of numerous text book teachings and the high level of skill in the art, real life chemistry remains unpredictable as described by Dorwald (see above). Further skilled artisan would not anticipate productive binding of structurally diverse compounds such as C1 and C2 in the same protein pocket.

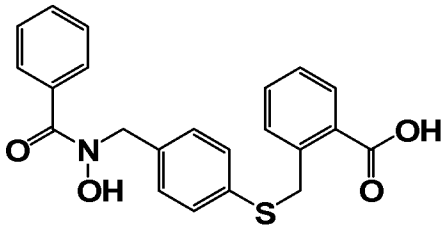
Guidance and Direction: See above section under response to Applicants Remarks.

The presence or absence of working examples. There are two working examples in the specification.

These are:



A



B

The specification also disclose two esters (iv and ix) corresponding to the two acids A and B. The specification claims that these esters may be prodrugs of the acids since they are hydrolyzed in cell assays. In these only examples present in the specification, major portions of the two compounds are the same, difference being the carboxylic acid containing substituents on the sulfur. However, the in vitro biological activity (Table-2) of the structurally these very similar compounds differ four fold. The difference in the activity of the corresponding esters iv and ix are even more substantial. Thus while iv provides about 28% inhibition at 2 micromolar IC50 concentration, ix is inactive at this concentration. Cell based assay data for these compounds are presented in the Table-3 page 57. Missing in this tables is the disclosure of the activity for compound A and missing IC50 for compound E. Compound ix is the presumed prodrug of E (See page 57, lines 24-26); however, compound ix is active with IC50 of 15 micormolar, E is inactive in this assay. Missing in this Table-3 is data for A that would have provided a modicum of guidance with respect to Structure Activity Relationships. Thus of the 4 compounds tested, of the billion possibilities, two had IC50s of 2

micromolar and 10 micromolar in the vitro assay. The prodrugs were deemed active in the cell proliferation assay (IC50s 8 micromolar and 15 micromolar, deemed significant see page 57 last paragraph). Further compound E deemed active in the in vitro assay (Table 2) is inactive in the cell proliferation assay (Table 3). In spite of the six replicates the activity of ix and E shown in Table-3 is inconsistent at best. Thus within the two compounds wherein major portions of the structure are identical, there is major difference in the activity which is consistent with the unpredictability in the art of biological chemistry. The unpredictability in the area of glyoxalase biology is particularly high. See Applicant provided reference P.J.Thornalley, Critical Reviews in Oncology/Hematology 20 (1995), 99-128 and references cited therein. Thornalley teaches that S-p-bromobenzylglutathione is potent competitive inhibitor of human glyoxalase with Ki of 160 nanomolar but it had no significant effect on the growth of HL60 cells. Further applicants use of the terms 'quantifiable biological effect' page 15 (remarks filed 10/01/2008) with regards to potency of the compounds in the two assays is consistent with current concepts of medicinal chemistry that such level of activity is at best starting point for optimization of structure for eventual use. The issue at hand is the assertion that the two compounds 'share a common core with a conserved substitution pattern'. (see page 16 lines 6-7). However, what actually are conserved are three structural moieties (that could be connected with the structurally broad divergent linkers). Thus even if the conservation of structural elements within A and E is acknowledged, one skilled in the art would not anticipate that molecules such as

C2 and A to bind to the same receptor pocket.

It is respectfully submitted that one skilled in the art of medicinal chemistry would regard the linking of three structural groups to achieve productive small molecule protein interaction as 'vague intimation of a general idea' because of the structural similarity within the two disclosed compounds in the context of the limited disclosure of their activity. *Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".*

The quantity of experimentation needed: It is acknowledged that the mere breadth of the claims does not necessarily require a conclusion that undue experimentation would be required to make and use the invention. However breadth is considered in conjunction with direction, guidance and working examples pertaining to:

a) claims to seemingly endless possibilities of widely *differing* structural templates (compare structures C1, C2, A and E shown above) alleged to bind to the same protein

b) disclosure of limited synthetic procedures

c) limited biological activity of two similar analogs and their alleged prodrugs showing inconsistent biological activity (compare activity Tables 2 and 3)

d) unpredictability in the area of chemical art and in particular pharmaceutical art relating to glyoxalase I.

e) lack of structural guidance for selection of embodiments

There is a substantial gap between what is taught in the specification and what is being claimed. Consequently, it is not clear what specific embodiments of the given formulae would have glyoxalase I inhibitory activity. As such, one of ordinary skill in the art would be faced with undue amount of experimentation to identify compound(s) buried in the zillion possibilities encompassed by the formulae. The specification lacks disclosure sufficient to make and use the invention commensurate with the scope of the claims.

MPEP 2164.01(a) states, “A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ 2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation would be required to make and use Applicants' invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NIZAL S. CHANDRAKUMAR whose

telephone number is (571)272-6202. The examiner can normally be reached on 8.30 AM - 4.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571 0272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nizal S Chandrakumar/
Examiner, Art Unit 1625

/D. Margaret Seaman/

Primary Examiner, Art Unit 1625